Clinical Applications: Vancomycin

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Introduction

• Renewed interest in 1980’s due to MRSA
  --> Increased understanding of the PK/PD
• Routine monitoring? Trough only?
• Nomogram or PK model?
Nephrotoxicity

- Related to trough $> 10\text{mg/L}$,
- Duration of therapy $> 21\text{ days}$,
- Concurrent nephrotoxic agents
- Older patient...
Nephrotoxicity

- Vancomycin alone
  5% (n=60)
- Vancomycin + aminoglycoside
  22% (n=63)

Rybak et al. JAC 1990;679-87
Ototoxicity

- Peaks > 80 mg/l?
- Concurrent ototoxic agents
- Duration of therapy > 21 days
- Older patient...
Figure 1. Serum vancomycin concentrations in patients in whom ototoxicity was noted. Patients 1 through 7 either did not use other ototoxic drugs or their use was not reported. Patients 8 through 10 were being treated for meningitis, and patients 11 through 17 received aminoglycosides and/or erythromycin in conjunction with vancomycin. Other = a level that is not a peak or trough.
Pharmacodynamics

- “Concentration-independent killing”
- Maximal activity at 5 x MIC [i.e. 10 mg/L]
- Higher concentrations for deep tissue infections
  - endocarditis, meningitis, osteomyelitis
- Continuous infusion?
FIG. 1. Concentration-versus-time profile of vancomycin. *, dosing regimen achieving a single peak of 48 μg/ml; ■, dosing regimen to achieve a peak of 30 μg/ml dosed again at 12 h; ▲, dosing regimen achieving a constant concentration of 16.2 μg/ml; ●, dosing regimen achieving a constant concentration of 8 μg/ml.
FIG. 2. Antibacterial effects of vancomycin, with different dosing regimens, against *S. aureus* ATCC 29213. +, control bacterial count in the absence of vancomycin; *, dosing regimen achieving a peak of 48 μg/ml; ×, dosing regimen achieving peaks of 30 μg/ml dosed again at 12 h; Δ, dosing regimen achieving a constant concentration of 16.2 μg/ml; ●, dosing regimen achieving a constant concentration of 8 μg/ml.
Dosing Methods

- Predictive performance: Nomograms vs. PK methods
  - 1 vs 2-compartment
  - Steady state vs non steady state
# Predictive Performance

<table>
<thead>
<tr>
<th>Methods</th>
<th>Peak ME</th>
<th>Peak MAE</th>
<th>Trough ME</th>
<th>Trough MAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moellering</td>
<td>-5.35</td>
<td>8.21</td>
<td>2.26</td>
<td>5.43</td>
</tr>
<tr>
<td>Matzke</td>
<td>-5.95</td>
<td>10.5</td>
<td>1.67</td>
<td>5.76</td>
</tr>
<tr>
<td>Sawchuk-Zaske</td>
<td>-2.53</td>
<td>4.61</td>
<td>-2.16</td>
<td>2.69</td>
</tr>
<tr>
<td>Bayesian</td>
<td>1.73</td>
<td>4.93</td>
<td>-0.67</td>
<td>2.73</td>
</tr>
</tbody>
</table>

Figure 19-4. Serum concentration-time profile of vancomycin at steady state. Difference between the peak concentrations at the end of infusion for two-compartment model (●) and one-compartment model (○).
# Prediction Error

(1-compartment model)

<table>
<thead>
<tr>
<th>Timing</th>
<th>$C_{\text{max}}$</th>
<th>$V_{\text{dss}}$</th>
<th>$T\frac{1}{2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25, 11</td>
<td>29.5 (-18)</td>
<td>0.44 (-37.7)</td>
<td>4.9 (-35.6)</td>
</tr>
<tr>
<td>0.5, 11</td>
<td>25.2 (-29.9)</td>
<td>0.54 (-23.3)</td>
<td>5.4 (-28.4)</td>
</tr>
<tr>
<td>1, 11</td>
<td>20.5 (-43)</td>
<td>0.72 (2.3)</td>
<td>6.4 (-16.1)</td>
</tr>
<tr>
<td>1.5, 11</td>
<td>18.5 (-48.6)</td>
<td>0.84 (19.4)</td>
<td>7.0 (-8.0)</td>
</tr>
<tr>
<td>3, 11</td>
<td>17.1 (-52.6)</td>
<td>0.95 (35.1)</td>
<td>7.5 (-0.8)</td>
</tr>
</tbody>
</table>

Two compartment parameters: Cmax 36 mg/L, Vdss 0.7 L/Kg, T1/2 7.6 h
2-Compartment Model

<table>
<thead>
<tr>
<th></th>
<th>ME</th>
<th>MAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>-3.2 (16.8)</td>
<td>12.1 (12)</td>
</tr>
<tr>
<td>Bayesian</td>
<td>0.0 (4.6)</td>
<td>3.6 (2.7)</td>
</tr>
</tbody>
</table>

Summary

- Routine Monitoring?
- Target trough
- 2-compartment Bayesian model
  - Peak/Trough required